Mrs. Archibald, a 92-year-old woman, has been a customer at your pharmacy for many years. When her son, Ken, comes in to pick up her monthly blister packs, you tell him that she’s been started on another medication and she now needs to use two blister packs daily to hold all of her 17 medications. Ken sighs heavily and says it’s hard to get her to take the medications she already has. She’s getting dizzy and confused, her nausea is worse, and she hardly eats. She’s had several falls recently and is now afraid to go out.

The elderly represent one of the fastest growing segments of the population and their use of medication is increasing significantly. In Ontario, from 1997–2006, the population older than 65 years of age increased by 18% while their claims to the provincial drug benefit program increased by 214%. The Canadian National Population Health Survey recently showed that 53% of seniors living in healthcare institutions, and 13% of those living in the community use five or more medications, with older seniors taking more medications than younger seniors. This is consistent with Canadian Institute for Health Information data that show 23% of those older than 65 years of age and 30% of those older than 85 years of age had claims for multiple medications, typically five or more. Recently, it has been used to describe the use of inappropriate medications, or more medications than clinically indicated. The prevalence of inappropriate medication use in the elderly ranges from 11.5%–62.5%. Consequences of polypharmacy include adverse drug reactions and interactions, nonadherence, increased risk of cognitive impairment, impaired balance and falls, and increased risk of morbidity, hospitalization, and mortality.

Age-Related Changes

With advancing age, progressive functional decline in organ systems (eg, kidney, liver) leads to changes in the way medications are handled and expressed. Pharmacokinetic changes are outlined in Table 1. As little pharmacokinetic data are available for the elderly, we must make assumptions about what drugs might be affected. Pharmacodynamic changes (ie, physiologic and biochemical effects of drugs on the body) with aging include increased sensitivity to cardiovascular medications, anticoagulants, opioid analgesics, antipsychotics, and benzodiazepines. Altered concentrations of neurotransmitters and receptors, as well as altered receptor binding properties and responsiveness, are thought to contribute to pharmacodynamic changes resulting in exaggerated drug effects. Functional reserves decline with age, affecting the cardiovascular, musculoskeletal, and central nervous systems; this...
can also predispose the elderly to exaggerated drug effects. Impaired homeostatic mechanisms can result in more pronounced side effects (eg, orthostatic hypotension with antihypertensives) or lack of compensatory responses (eg, impaired reflex tachycardia, impaired regulation of temperature and electrolytes). Patients previously stabilized on certain doses of medications may gradually begin to develop side effects over time because of these various changes. These side effects may be mistaken for new diseases, with new medications added for treatment.

**Lack of Evidence for Medication Use in the Elderly**

The elderly are underrepresented in drug trials, yet they are the greatest consumers of medications. A study examining randomized controlled trials of four commonly used medications found that the proportion of older patients (> 65 years) enrolled was significantly lower than the proportion in the average population; of 155 trials, only three dealt exclusively with the elderly. Despite the higher prevalence of many conditions (eg, hypertension, diabetes) in the elderly, exclusion criteria limit their enrollment in trials. The “healthy elderly” subjects included in clinical trials do not represent the population that would typically use these medications. Therefore, despite the wealth of guidelines available for chronic disease states (eg, hypertension, diabetes, cardiovascular disease), few specifically address how to approach the very old or frail elderly. Adhering to guidelines often results in the addition of medications without considering remaining life expectancy, goals of care, and time to potential benefit of medications.

**Strategies for Reducing Polypharmacy**

Pharmacists can take many practical and relatively easy steps to help reduce polypharmacy and promote medication adherence. Conducting a medication review for an older person taking many medications can be challenging but rewarding. Providing education and medication reduction suggestions to prescribers can reduce the overall number of medications and inappropriate medications.

**Step 1. Determine “Can This Be Caused by a Drug?”**

One of the simplest ways to address polypharmacy is to use screening tools to help identify potentially inappropriate medications (PIMs) in the elderly: medications with no clear evidence-based indications; medications that carry a substantially higher risk of adverse effects; or medications that are not cost-effective. Two commonly used screening tools are the Beers and STOPP criteria (Table 2), which differ slightly in content and sensitivity for detecting drug-related problems. They can be applied manually by visually comparing a patient’s medication list to each set of criteria or they can be incorporated into clinical decision support systems that flag PIMs at the time of prescribing. Stopping medications is an effective and safe approach to reducing polypharmacy.

Interventions such as computerized decision-support systems and pharmacist involvement in multidisciplinary teams (eg, geriatric medicine services) can also positively affect prescribing.

### Table 1. Pharmacokinetic Changes with Age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Decreased active transport decreases bioavailability for some drugs</td>
<td>Calcium with achlorhydria</td>
</tr>
<tr>
<td></td>
<td>Reduced first-pass metabolism (reduced liver mass and blood flow) increases bioavailability of some drugs</td>
<td>Metoprolol, Propranolol, Nortriptyline, Calcium channel blockers, Tricyclic antidepressants</td>
</tr>
<tr>
<td>Distribution</td>
<td>Increased body fat prolongs half-life of fat-soluble drugs</td>
<td>Diazepam, Amitriptyline</td>
</tr>
<tr>
<td></td>
<td>Decreased body water increases serum concentration of water-soluble drugs</td>
<td>Digoxin, Levodopa, Morphine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic disease or reduced hepatic volume and blood flow results in reduced oxidative metabolism (reduced metabolism through CYP450) and higher steady-state concentrations of some drugs</td>
<td>Diazepam, Metoprolol, Phenytoin, Theophylline, Alprazolam</td>
</tr>
<tr>
<td>Excretion</td>
<td>Decreased cardiac output (eg, in heart failure) results in less perfusion of kidneys and liver, which reduces elimination of high extraction ratio drugs</td>
<td>Imipramine, Morphine, Propranolol</td>
</tr>
<tr>
<td></td>
<td>Reduced kidney function reduces elimination of renally excreted drugs or metabolites</td>
<td>Digoxin, Cephalexin, Morphine, Meperidine, Gabapentin, Sotalol, Lisinopril, Ramipril, Diuretics, Metformin</td>
</tr>
</tbody>
</table>

Ken is clearly worried about his mom. You wonder whether her recent symptoms could be drug induced. You offer to take a closer look to see if any medications might be causing problems and whether her regimen can be simplified. You book an appointment to visit her mom at home and Ken happily pays the fee. He says having someone review all of her medications and work with the family doctor would be a great help.
that may contribute to common geriatric presentations are outlined in Table 3. Keep in mind that some side effects can manifest gradually as the result of a medication, whether it is a PIM or not, is a key step in determining which drugs might be causing problems. Linking potential pharmacology of each drug, its known side effects, and the time of onset side effects with causative drugs requires knowledge of the "therapeutic thought process" developed by Winslade and Bajcar. 

Drugs

Table 3. Common Geriatric Presentations That Can Be Caused by Drugs

<table>
<thead>
<tr>
<th>Signs or Symptoms</th>
<th>Common Drug-Related Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>Sedatives, hypnotics, anticholinergics, antihypertensives, antidepressants, antidiabetics (10,42,43)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Anticholinergics, benzodiazepines, antihistamines, tricyclic antidepressants (44,45)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Alpha-blockers, antidepressants, sedatives (eg, benzodiazepines), diuretics (46)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Anticholinergics, opioids, tricyclic antidepressants, calcium channel blockers, calcium supplements (47)</td>
</tr>
<tr>
<td>Delirium</td>
<td>Antidepressants, antipsychotics, antiepileptics (48)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Antibiotics, proton pump inhibitors, allopurinol, selective serotonin reuptake inhibitors, angiotensin II receptor blockers, psycholeptics (anxiolytics, antipsychotics) (49)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Nonsteroidal anti-inflammatory drugs, oral anticoagulants (50)</td>
</tr>
</tbody>
</table>

You think about Mrs. Archibald's recent symptoms—dizziness, falls, confusion, and nausea—and believe they might be related to her medications. Lorazepam could be causing dizziness, confusion, and falls. The many antihypertensive medications she is taking can all reduce blood pressure, which might result in dizziness, and hence falls. With a few questions, you determine that the nausea started soon after her metformin dose was increased. That's when the metoclopramide was started. Is this a prescribing cascade?

Prescribing cascades occur as a result of treating side effects of medications. For example, furosemide prescribed for a patient might cause urinary frequency. Oxybutynin is prescribed to manage the urinary frequency. Oxybutynin leads to confusion and behavioural disturbances and an antipsychotic is prescribed. As the list of medications grows, it becomes more difficult to sort out which medications were prescribed to treat medical syndromes as opposed to drug-related adverse effects. Ultimately, the cumulative effects of multiple medications can lead to more serious complications (eg, falls, delirium). Identifying and dealing with prescribing cascades requires a thorough history, including the timing of new symptom onset in relation to medication starts or changes. Table 4 lists some common prescribing cascades the authors have seen in practice.

Step 2. Determine Which Drugs Are Still Providing Benefit

Determining which medications are still providing benefit can be more challenging than identifying PIMs. This is an important step in the pharmacotherapy workup described by Cipolle et al. A good initial approach is to ask about the symptoms (eg, pain, sleep) for which each symptom-based drug is being used. Next, look at signs (eg,
Assessing the continued benefit of preventive medications is likely the hardest step. As noted earlier, few clinical trials included frail elderly individuals, so we know little about benefit versus risk in this population. For example, in situations of no other compelling indication (eg, angina, atrial fibrillation), the proven benefit of a beta-blocker post-myocardial infarction, in terms of reducing cardiovascular mortality, has been shown for only two years, yet guidelines recommend indefinite therapy.\(^{37}\) Appropriate duration of treatment for acute conditions is also often unclear. For example, four to eight weeks of proton pump inhibitor therapy is adequate for uncomplicated reflux or ulcers, yet many patients take them daily for years.

**Table 4. Examples of Prescribing Cascades**

- Ibuprofen → hypertension → antihypertensive
- Metoclopramide → parkinsonism → levodopa/carbidopa
- Risperidone → parkinsonism → benzotropine
- Amlodipine → edema → furosemide
- Gabapentin → edema → furosemide
- Ciprofloxacins → delirium → risperidone
- Lithium → tremor → propranolol
- Bupropion → insomnia → mirtazapine
- Donepezil → urinary incontinence → oxybutynin
- Amiodarone → tremor → lithium
- Venlafaxine → tremor → diazepam
- Meperidine → delirium → risperidone
- Beta-blocker → depression → antidepressant
- Amitriptyline → decreased cognition → donepezil
- Narcotic → constipation → sennosides
- Sennosides → diarrhea → loperamide
- Lorazepam → morning drowsiness → caffeine
- Enalapril → cough → dextromethorphan
- Furosemide → hypokalemia → potassium supplement
- Nonsteroidal anti-inflammatory drug → heartburn → H₂-antagonist or proton pump inhibitor
- Omeprazole → low B12 → B12 supplement

**Table 5. Drugs Commonly Associated With Adverse Drug Withdrawal Events\(^{58,59}\)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested Monitoring for Withdrawal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodipine</td>
<td>↑ BP, ↓ heart rate, NSAIDs—nonsteroidal anti-inflammatory drugs, PPIs—proton pump inhibitors, PRN—as needed, SOBOE—shortness of breath on exertion, ↑—increase, ↓—decrease</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Anxiety, depression, seizures</td>
</tr>
<tr>
<td>Antidepressants (eg, citalopram, venlafaxine, mirtazapine, amitriptyline)</td>
<td>Early: chills, malaise, sweating, irritability, insomnia, headache, Late: depression recurrence</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Insomnia, restlessness, hallucinations, nausea</td>
</tr>
<tr>
<td>Bcl-blockers</td>
<td>Agitation, confusion, nightmares, ↑ spams or rigidity</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>↑ HR, ↑ BP, angina, anxiety</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anorexia, ↓ BP, nausea, weakness, ↓ blood glucose</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Palpitations, ↑ HR</td>
</tr>
<tr>
<td>Diuretics (eg, furosemide, hydrochlorothiazide)</td>
<td>↑ Pedal edema, chest sounds, SOBOE, ↑ weight</td>
</tr>
<tr>
<td>Gabapentin (eg, for pain)</td>
<td>↑ Pain, ↑ PRN use, mobility changes</td>
</tr>
<tr>
<td>Hypnotics (eg, lorazepam, zopiclone)</td>
<td>Poor sleep, ↑ anxiety, agitation, tremor</td>
</tr>
<tr>
<td>Narcotics</td>
<td>↑ Pain, ↑ PRN use, mobility changes, insomnia, anxiety, diarrhea</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↑ Pain, ↑ PRN use, mobility changes</td>
</tr>
<tr>
<td>PPIs, domperidone</td>
<td>Rebound heartburn, indigestion</td>
</tr>
<tr>
<td>Transdermal nitroglycerin</td>
<td>Angina, ↑ BP</td>
</tr>
</tbody>
</table>

**Step 3. Prioritize Drugs for Tapering and Stopping, Develop a Plan, Coordinate and Communicate with Prescriber and Patient**

When deciding which medications to stop first, it is important to balance clinical impact (eg, reduction in side effects) with the risk of adverse drug withdrawal events (ADWEs, defined as clinically significant signs or symptoms caused by stopping a drug).\(^{58}\) They can manifest as physiologic withdrawal reactions (eg, tachycardia with beta-blocker discontinuation), appearance of new symptoms (eg, sweating with antidepressant withdrawal), or exacerbation of an underlying condition (eg, worsening angina after stopping nitrates).\(^{58}\) Table 5 lists drugs that often have ADWEs. Factors that make ADWEs more likely are long duration of use (eg, benzodiazepines), higher dose (eg, corticosteroids), and short half-life (eg, paroxetine). Patient risk factors include a history of drug dependence or abuse and lack of buy-in. Certain medications are often tapered to reduce the incidence and severity of ADWEs. To successfully discontinue unnecessary or inappropriate medications, it is important to know which drugs can be stopped abruptly and those that should be tapered.

It can be challenging to get patient and prescriber acceptance of the need to reduce medication dose, or discontinue or “depresscribe” unnecessary medications. Patient buy-in is important; in the absence of any acute adverse medication effects, collaboration with the patient can assist in deciding which medications to stop first. Asking a few simple questions can facilitate this process:

- What questions do you have about your medications?
- Which medications do you feel most strongly about keeping?
Mrs. Archibald repeats that the metoclopramide does not help her nausea. Her appetite is terrible and she does not want to go out with friends. She wants to keep acetaminophen—it effectively treats her knee pain and helps her get around the house. Her diabetes, diagnosed three years ago, is not a big bother; she doesn’t think she needs all that medication. You start preparing a note to Mrs. Archibald’s family physician. It’s important to inform the physician that metoclopramide did not improve Mrs. Archibald’s nausea. You suggest lowering the dose gradually and stopping metoclopramide over the next couple of weeks. Metoclopramide would be a good medication to prioritize tapering because of its potential to cause Parkinson-type symptoms (which you learned from the Beers and STOPP criteria). You include in your note that Mrs. Archibald’s nausea started soon after the metformin dose was increased, which coincided with her starting to take all of her diabetes medications again; it is severely affecting her quality of life. You note her recent low blood sugars and suggest reducing metformin back to the previous dose and switching glyburide to an equivalent dose of once-daily gliclazide MR to reduce the risk of hypoglycemia. You note that you will ask Mrs. Archibald to continue to monitor her nausea and blood glucose, and you will update the physician with changes.

When preparing patients for medication discontinuation, make sure to offer safer alternatives, including nonpharmacologic approaches (eg, distraction techniques for pain management, sleep hygiene approaches instead of sedatives). Prepare patients by discussing anticipated withdrawal effects and involve them in monitoring for ADWEs. Let the patient know that several attempts at withdrawal may be needed. Regular follow-up will also provide support and reassurance. Use a variety of communication tools including verbal and written, and use tapering calendars for more complicated cases.

After successfully stopping metoclopramide and eliminating the nausea and low blood sugar readings by reducing the metformin dose and changing from glyburide to gliclazide, Mrs. Archibald calls to thank you. She is still dizzy, tired, and confused during the day and wonders if her medications might be the cause. Her low blood pressure, as well as lorazepam, might be contributing. When you mention the latter, she says no one has ever told her that sleeping pills might cause confusion. She tried to stop them once, but had trouble sleeping so she just kept taking them. You explain the natural history of rebound insomnia and that it improves within days of stopping. She’s willing to try again and agrees to taper the dose. You call to update the family physician about this plan. You also discuss using a higher blood pressure target range, especially in light of her hypotension and dizziness. Her physician agrees to begin tapering doses of her antihypertensives. With the agreement of the patient and family physician, you email a lorazepam and antihypertensive tapering schedule to Mrs. Archibald’s family physician. It’s important to inform the physician that Mrs. Archibald’s hypoglycemia has coincided with her starting to take all of her diabetes medications again; it is severely affecting her quality of life. You note her recent low blood sugars and suggest reducing metformin back to the previous dose and switching glyburide to an equivalent dose of once-daily gliclazide MR to reduce the risk of hypoglycemia. You note that you will ask Mrs. Archibald to continue to monitor her nausea and blood glucose, and you will update the physician with changes.

**Table 6. Key Resources for Individualizing Therapy and Reducing Polypharmacy in the Elderly**

- Beers Criteria and STOPP (Screening Tool of Older Person’s Prescriptions) Criteria (see Table 2)
- Rx Files: Drug treatment in the elderly and long-term care. Available from www.rxfiles.ca/rxfiles/Modules/ltc/ltc.aspx
- Palliative Geriatric Practice algorithm: Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med 2010;170:1648-54
- Cruz-Jentoft A, Boland B, Rexach L. Drug therapy optimization at the end of life. Drugs Aging 2012;29:511-21
- Recommended journals:
  - Drugs and Aging
  - Age and Aging
  - Clinics in Geriatric Medicine

**Step 4. Simplify to Reduce Pill Burden**

Pill burden usually refers to the total number of pills or doses a patient must swallow during the day. Mrs. Archibald’s original 17 medications carried a pill burden of 36 tablets or capsules daily. Complex regimens and poor timing or unnecessary separation of multiple medications can lead to errors in medication administration; they may also affect quality of life, as patients feel they cannot vary from their strict regimen and sometimes feel too full of medication to eat. Patients may complicate high pill burden regimens by creating more complex dosage schedules (eg, 7 times a day instead of qid), especially when medication instructions vary in wording (eg, twice daily vs every 12 hours). Stopping or tapering unnecessary medications decreases the potential for adverse drug events and interactions; it also reduces pill burden, which may simplify medication scheduling.
Once unnecessary and side-effect causing medications have been stopped, steps to further reduce pill burden and enhance adherence include using combination products (eg, diuretic + another antihypertensive; cholesterol-lowering drug + antihypertensive; two hypoglycemics) or switching from multiple-times-daily to once-daily formulations.\(^{63,62}\)

**After checking with Mrs. Archibald every couple of weeks and working closely with her family doctor, your patient has been able to stop lorazepam and significantly reduce her antihypertensives. By combining several medications, you’ve reduced her number of medications to 9 and her pill burden to 16, now taken twice daily instead of four times daily—with only one blister pack! She is feeling much better, eating normally, and has started going out again to her various activities.**

**Conclusion**

Polypharmacy is a growing problem in scope and impact. By 2036, one in four Canadians will be older than 65 years of age; this growing demographic is at risk for drug therapy problems.\(^{63}\) With recent regulatory and reimbursement changes, pharmacists are even more well-placed to actively participate in optimizing therapy in the elderly. Helpful resources to assist pharmacists in individualizing therapy and reducing polypharmacy in the elderly are presented in Table 6. Pharmacists must share responsibility with prescribers and patients to ensure that potentially inappropriate medications are minimized, appropriate medications and doses are used, side effects are not treated with more medication without first investigating medication-related causes, and pill burden is minimized.

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